DERIVATIVES OF THE ANDROSTANE SERIES

XVII. Steroido[3, 2-c]pyrazoles

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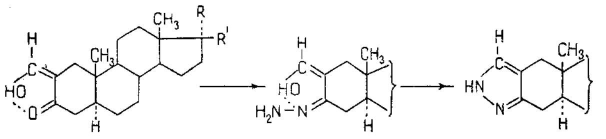
In the last few decades, anabolic steroids have been used in the treatment of various diseases connected with a disturbance of the nitrogen balance. An important position among them is occupied by steroids with condensed heterocyclic nuclei [1].



I R = H; R' = OH,

II R = H; R' = iso = C_8H_{17}

This paper gives the results of a study of the mechanism of the reaction of 2-hydroxymethylene-3-oxosteroids having various substituents at C_{17} with hydrazine hydrate in ethanol. We have investigated 2-hydroxymethylenedihydrotestosterone (I) and 2-hydroxymethylenecholestanone (II). It was found that, in analogy to what has been reported [2], the corresponding 3-hydrazones first separated out.

The IR spectra of the hydrazones obtained showed the presence of characteristic frequencies of the following groups (cm^{-1}): 1625, 1590 (C=C), (C=N), 3324, 3180 (NH_2). The low values of the frequencies of the stretching vibrations of the primary amine group are connected with the presence of a hydrogen bond [3].

The UV spectra of these hydrazones have strong absorption in the 229 mμ region, which characterizes the contraction of the hydrogen cloud at C_3 on passing from C=O to C=N when the system of double bonds is conjugated. The isolated carbonyl group, giving an absorption maximum at 281–284 mμ in the initial 2-hydroxymethylene-3-oxosteroids, disappears under the action of hydrazine hydrate. Thus, it may be concluded that the hydroxymethylene group at C_2 does not rearrange into an aldehyde group under the conditions of the action of hydrazine hydrate and of the isolation of the 3-hydrazone but remains in the form of a hydroxymethylene group with the retention of a hydrogen bond. In the subsequent stage of the synthesis of the steroidopyrazoles, the 3-hydrazones are heated in vacuum, water splits out, and the hydrazones undergo ring-closure with the formation of a pyrazole ring.

To investigate the influence of the temperature on the substances isolated in this synthesis, we have studied the reaction at 140–150° C in ethylene glycol. Under these conditions, 2-hydroxymethylenedihydrotestosterone and 2-hydroxymethylenecholestanone gave substances with mp 203–206° C and 240–242° C, respectively, the properties and spectral characteristics of which coincided completely with those of 17β-hydroxyandrostano[3, 2-c]pyrazole and of cholestano[3, 2-c]pyrazole [4, 5]. Consequently, under these conditions the formation of the 3-hydrazono-2-hydroxymethylenesteroid is accompanied by its rapid dehydration so that the steroidopyrazoles are formed.

EXPERIMENTAL

The initial 2-hydroxymethylenedihydrotestosterone and 2-hydroxymethylenecholestanone were synthesized by methods described previously [6, 7].

17β-Hydroxyandrostano[3, 2-c]pyrazole. A mixture of 2 g of 2-hydroxymethylenedihydrotestosterone, 7 ml of hydrazine hydrate, and 15 ml of methanol was boiled for 5 hr and was then diluted with 200 ml of water and left until the following day. Then the precipitate was filtered off, washed with water, dried at room temperature, heated with 50 ml of ether, filtered off, and dried in a desiccator at room temperature to constant weight. This gave 1.3 g of

3-hydrazono-2-hydroxymethylenedihydrotestosterone with mp 135–138° C; λ_{max} 230–231 mμ. IR spectrum, cm^{-1}: 1544, 1625, 3177, 3324.

The 3-hydrazone obtained was heated in a vacuum of 5–7 mm at 140–150° C for 6 hr. Dehydration in this way yielded 1.23 g (62.5% of theory) of 17β-hydroxyandrostano[3, 2-c]pyrazole with mp 213–215° C; λ_{max} 229 mμ. IR spectrum, cm^{-1}: 1336, 1444, 1560. Literature data: mp 217–225° C; λ_{max} 224 mμ [1].

Cholestano[3, 2-c]pyrazole. The reaction of 2 g of 2-hydroxymethylenecholestanone and 7 ml of hydrazine hydrate under the conditions of the preceding experiment gave 1.9 g of 3-hydrazono-2-hydroxymethylenecholestanone with mp 232–234° C, λ_{max} 231 mμ. IR spectrum; cm^{-1}: 1340, 1590, 3110, 3224.

The similar heating in vacuum of the 3-hydrazone obtained yielded 1.78 g (91.0% of theory) of cholestano[3, 2-c]pyrazole with mp 235–238° C; λ_{max} 230–231 mμ. IR spectrum, cm^{-1}: 1340, 1370, 1444, 1598.

Found, %: N 7.12. Calculated for $C_{28}H_{46}N_2$, %: N 7.02.

Literature data: mp 220.2–228.6° C; λ_{max} 225 mμ [4].

CONCLUSIONS

1. The synthesis of 17β-hydroxyandrostano[3, 2-c]pyrazole and of cholestano[3, 2-c]pyrazole has been effected by the reaction of the corresponding 2-hydroxymethylene-3-oxosteroids with hydrazine hydrate.

2. The mechanism of the formation of these pyrazoles has been studied. It has been shown that the reaction takes place in two stages, regardless of the substituent at C_{17} of the steroid molecule, with the formation of the 2-hydroxymethylene-3-hydrazone and its dehydration to form the pyrazole derivative.

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